

REMARKS

The Examiner has acknowledged Applicants' election of the invention of Group I (claims 1-102), as well as the election of Species Ia (claims 1-14, 16-80, 83-90, 92 and 94-102) and Species I-5 (claims 1-42, 60-83 and 89-102). However, in the Claim Status section of the pending Office Action, the Examiner has summarily withdrawn claims 27-32, 35-59, 78-79, 81-88 and 91-93, citing 37 C.F.R. 1.142(b). Applicants traverse the withdrawal of these claims as they were not unelected as required by 37 C.F.R. 1.142(b). Applicants are confused as to why these claims were withdrawn. All of the claims withdrawn by the Examiner depend from independent claims that belong to the elected claims of Group I, and claims that were not withdrawn by the Examiner (claims 1, 18 and 67). Applicants respectfully request clarification on the status of the claims. For the purposes of responding to the pending Office Action, Applicants assume that claims 1-102 constitute the pending claims currently under consideration in the present application. Applicants acknowledge that claims 103-157 are withdrawn from consideration as directed to a non-elected invention.

Applicants cancel, without prejudice, claims 43-44, 70 and 84. Applicants reserve the right to pursue any canceled subject matter in this application or applications that relate to the present application.

Applicants have amended claims 1-4, 6-9, 11, 14, 15-18, 20, 22, 25-26, 33-34, 36-38, 42, 45, 47, 57, 59-64, 65-67, 69, 71, 73-81, 85-99, and 101-102 merely to improve their form and to correct grammatical and typographical errors. Claims 1, 18, and 67 have been amended to more particularly point out certain aspects of Applicants' invention. Specifically, claims 1, 18 and 67 have been amended to specify that the recited stem cell is an inner mass cell, an embryonic stem cell, an embryonic germ cell, an embryoid body cell, a morula-derived cell, or a partially differentiated embryonic stem cell. Support for the claim amendment can be found throughout the specification and claims as filed. For example, support can be found at paragraph 59 of the present specification (see U.S. Patent Publication No. 2004/0219563). Claim 1 has also been amended to include the step of correlating a change in the level of expression of a marker DNA construct with the differentiation of a cell. Support for the claim amendment can be found throughout the specification and claims as filed. For example, support can be found at paragraphs 33, 42, 116 and 148 of the present specification (see U.S. Patent Publication No. 2004/0219563).

Additionally, Applicants have added new claim 158. Support for the subject matter of the newly added claim can be found throughout the specification and claims as filed. For example, support can be found at paragraph 59 of the present specification (see U.S. Patent Publication No. 2004/0219563).

Applicants' amendments and newly added claim are fully supported by the specification. No new matter has been added. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

1. Claim 16 is objected to because it contains the typo "screeding". Applicants have corrected this typographical error. Applicants' correction of this obvious typographical error does not narrow the scope of claim 16. Claim 67 is objected to because it contains a duplication of the word "genes". Applicants have corrected this typographical error. Applicants' correction of this obvious typographical error does not narrow the scope of claim 67. Claim 70 is objected to as allegedly being of improper dependent form for failing to further limit the subject matter of its antecedent claim. Applicants have canceled claim 70. In view of the foregoing amendments, the Examiner's objections to claims 16, 67 and 70 are moot.

2. Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, for allegedly being incomplete for omitting essential steps, such omission amounting to a gap between the steps. The Examiner alleges that there is a disconnect between the preamble and outcome of the method of the rejected claims. Applicants traverse this rejection and contend that the rejection is moot in view of the amended claims.

Claim 1 and dependent claims 2-17 recite a method for determining the relative timing of the transcriptional activation or repression of a gene in a stem cell that occurs when the stem cell differentiates. Applicants contend that no essential steps are omitted in the rejected claims. Nevertheless, to expedite prosecution, Applicants have amended the claims to more particularly point out certain embodiments of the invention. Specifically, Applicants have amended claim 1 so that the method includes correlating a change in the level of expression of a marker DNA construct with the differentiation of a stem cell. This amendment makes clear that the recited method is useful for determining the relative timing of the change in the level of expression of a

gene in a differentiating stem cell. Applicants' amendment is not in acquiescence to the rejection. Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection are respectfully requested.

Claim 64 is rejected under 35 U.S.C. 112, second paragraph, as indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleges that the rejected claim is indefinite because the claim contains a blank at the end of the claim. Applicants have amended claim 64 to remove the blank, thereby obviating the rejection. Applicants' amendment is made solely to correct an obvious clerical error and does not alter the scope of the claim. Reconsideration and withdrawal of this rejection are respectfully requested.

3. Claims 1-8, 16-26, 60-69, 71, 90, and 94-96 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by Stanford *et al.* (Blood, 92(12):4622-4631 (1998); hereinafter "Stanford 1"). Applicants traverse this rejection and contend that the rejection is moot in light of the amended claims.

Applicants respectfully disagree with this rejection on the grounds that the Stanford 1 reference does not disclose all of the elements of the rejected claims, particularly the claims as amended. Applicants submit that a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference (see MPEP 2131). As amended, claim 1, and dependent claims 2-8, 16-26, 60-69, 71, 90 and 94-96, are directed to the determination of the transcriptional regulation of a marker DNA in a human stem cell when the stem cell differentiates, wherein the stem cell is an inner mass cell, an embryonic stem cell, an embryonic germ cell, an embryoid body cell, a morula-derived cell, or a partially differentiated embryonic stem cell. Stanford 1 generally relates to murine embryonic stem cells containing *lacZ*. Nowhere does Stanford 1 teach or suggest a marker DNA in human stem cells. Further, Stanford 1 fails to teach or suggest the determination of the transcriptional regulation of a marker DNA in human stem cells when the human stem cells differentiate. These deficiencies of Stanford 1 were recognized and acknowledged by the Examiner in the pending Office Action (see page 8, last paragraph of the outstanding Office Action). Accordingly, Stanford 1 fails to anticipate the claimed invention.

Applicants' amendment is not in acquiescence to the rejection and is made solely to expedite prosecution. Applicants reserve the right to prosecute claims of similar or differing scope. The cited reference fails to teach or suggest each and every limitation of the claimed invention, and thus the cited reference fails to satisfy the criteria necessary for anticipating the claimed invention. Reconsideration and withdrawal of this rejection is respectfully requested.

As Applicants note above in the section of the instant response discussing the status of the claims, Applicants contend that the Examiner has erroneously withdrawn claims 27-32, 35-59, 78-79, 81-88 and 91-93, and that these claims are also presently under consideration. However, given that the Examiner temporarily withdrew claims 27-32, 35-59, 78-79, 81-88, and 91-93 from consideration, the Examiner did not indicate whether or to what extent he would apply the instant rejection to any of these claims. Nevertheless, Applicants note for the record, that the foregoing arguments regarding the patentability of the claimed invention in view of Stanford 1 apply at least equally to temporarily withdrawn claims 27-32, 35-59, 78-79, 81-88, and 91-93. As such, all of the pending claims directed to the elected invention of Group 1 are patentable over Stanford 1 for, at least, the reasons outlined above. Given that Stanford 1 fails to teach or suggest each and every limitation of the claimed invention, Stanford 1 fails to satisfy the criteria necessary for anticipating the claimed invention.

4. Claims 1-8, 10, 16-26, 60-76, 90, 92 and 94-100 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Stanford 1 in view of Nehls *et al.* (U.S. Patent 6,218,123; hereinafter "the '123 patent"). Applicants respectfully traverse this rejection and contend that the rejection is moot in view of the amended claims.

Pursuant to MPEP 2142, "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

Applicants contend that the cited references fail to satisfy the criteria necessary to render the claimed invention obvious. Nevertheless, to expedite prosecution, Applicants have amended claims 1, 18, 67 (and claims dependent thereon) to more particularly point out certain embodiments of Applicants' invention. Specifically, Applicants have amended the claims to more particularly point out that the methods and compositions of the invention relate to human stem cells. As amended, the claims are directed to the determination of the transcriptional regulation of a marker DNA in a human stem cell when the stem cell differentiates, wherein the stem cell is an inner mass cell, an embryonic stem cell, an embryonic germ cell, an embryoid body cell, a morula-derived cell, or a partially differentiated embryonic stem cell.

The cited references fail to teach or suggest the subject matter of the amended claims. As stated above, Stanford 1 does not teach or suggest a marker DNA in human stem cells, and particularly the determination of the transcriptional regulation of a marker DNA in human stem cells when the human stem cells differentiate. The '123 patent fails to cure this deficiency.

The Examiner alleges that the '123 patent teaches, *inter alia*, methods of screening gene trap cassettes integrated into the genome comprising selectable markers, including chromogenic and fluorescent markers, and that "the gene trap selection method is employed ... [on] ... preferred target cells include ... embryonic stem cells, and particularly human embryonic or other stem cells." Applicants disagree with the Examiner's characterization of the '123 patent. The '123 patent relates to the construction of cDNA libraries from cultured eukaryotic cells (see abstract and column 1, lines 8-10). The '123 patent uses recombinant constructs that randomly insert into the genome merely to facilitate the expression of nuclear genes in a given state (see column 1, lines 10-13). The '123 patent does not teach the determination of the transcriptional regulation of a marker DNA in human stem cells, especially when the human stem cells differentiate. The Examiner acknowledges this point in the pending Office Action (see page 9, fourth paragraph of the outstanding Office Action). Accordingly, Applicants contend that the combined teachings of Stanford 1 and the '123 patent fail to satisfy the criteria necessary to render the claimed invention obvious.

The second and third criteria for assessing obviousness are that there must be some suggestion or motivation to modify the reference or to combine reference teachings, and that one of skill in the art would have a reasonable expectation of successfully modifying the references to arrive at the claimed invention. As stated above, taken as a whole, the '123 patent teaches the

construction of cDNA libraries from cultured eukaryotic cells using recombinant constructs that randomly insert into the genome merely to facilitate the expression of nuclear genes in a given state (see column 1, lines 8-13). In contrast, the present application provides methods for determining the regulation of a marker DNA in human stem cells when they differentiate. Given the disparate purposes of the technologies disclosed in these two references, one of skill in the art setting out to produce the claimed invention would have had neither the motivation nor the reasonable expectation of successfully combining the teachings of Stanford 1 and the '123 patent in an attempt to arrive at the claimed invention.

Applicants take this opportunity to clarify the record with respect to the alleged teachings of Stanford 1. In the outstanding Office Action, the Examiner states that Stanford 1 teaches that gene trap analysis of human embryonic stem cell gene expression is important for understanding normal physiological processes and human disease (see page 10, second paragraph of the outstanding Office Action). Applicants respectfully clarify that Stanford 1 teaches that insights in the use gene trap analysis in murine cells may merely serve as a model for understanding human disease (see page 4622, column 1). Stanford 1 does not teach or suggest gene trap analysis of human embryonic stem cell gene expression itself, as the Examiner suggests. Rather, the Examiner's broad interpretation of the teachings of Stanford 1 appears to reflect an appreciation of the present invention and subsequent advances in the stem cell arts, and not on the Stanford reference itself. Such an interpretation leaves Applicants vulnerable to an obvious rejection based on impermissible hindsight.

Applicants' amendment is not in acquiescence to the rejection. Applicants reserve the right to prosecute claims of similar or differing scope. The cited references fail to teach or suggest each and every limitation of the claimed invention, and thus the cited references fail to undermine the patentability of the claimed invention. Reconsideration and withdrawal of this rejection are respectfully requested.

As Applicants note above in the section of the instant response discussing the status of the claims, Applicants contend that the Examiner has erroneously withdrawn claims 27-32, 35-59, 78-79, 81-88 and 91-93, and that these claims are also presently under consideration. However, given that the Examiner temporarily withdrew claims 27-32, 35-59, 78-79, 81-88, and 91-93 from consideration, the Examiner did not indicate whether or to what extent he would apply the instant rejection to any of these claims. Nevertheless, Applicants note for the record,

that the foregoing arguments regarding the patentability of the claimed invention in view of the combined teachings of Stanford 1 and the '123 patent apply at least equally to temporarily withdrawn claims 27-32, 35-59, 78-79, 81-88, and 91-93. As such, all of the pending claims directed to the elected invention of Group 1 are patentable over Stanford 1 and the '123 patent for, at least, the reasons outlined above. The combined teachings of Stanford 1 and the '123 patent fail to satisfy the criteria necessary to undermine the patentability of the claimed invention.

Claims 1-10, 16-26, 60-69, 71, 77, 80, 90, 94-96 and 101-102 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Stanford 1 in view of Stanford *et al.* (Nature Reviews Genetics, 2:756-768 (2001); hereinafter "Stanford 2"). Applicants traverse this rejection and contend that the rejection is moot in view of the amended claims.

Applicants contend that the cited references fail to satisfy the criteria necessary to render the claimed invention obvious. Nevertheless, to expedite prosecution, Applicants have amended claims 1, 18, 67 (and claims dependent thereon) to more particularly point out certain embodiments of Applicants' invention. Specifically, Applicants have amended the claims to more particularly point out that the methods and compositions of the invention relate to human stem cells. As amended, the claims are directed to the determination of the transcriptional regulation of a marker DNA in a human stem cell when the stem cell differentiates, wherein the stem cell is an inner mass cell, an embryonic stem cell, an embryonic germ cell, an embryoid body cell, a morula-derived cell, or a partially differentiated embryonic stem cell. The cited references fail to teach or suggest the subject matter of the amended claims.

As detailed above, Stanford 1 does not teach or suggest a marker DNA in human stem cells, and particularly the determination of the transcriptional regulation of a marker DNA in human stem cells when the human stem cells differentiate. Stanford 2 fails to cure this deficiency. Similar to Stanford 1, Stanford 2 generally relates to murine embryonic stem cells. Nowhere does Stanford 2 teach or suggest a marker DNA in human stem cells. Therefore, the combined teachings of the cited references fail to undermine the patentability of the rejected claims.

In addition, one of skill in the art setting out to produce the claimed invention would have had neither the motivation nor the reasonable expectation of successfully combining the teachings of Stanford 1 and Stanford 2 in an attempt to arrive at the claimed invention. Human embryonic

stem cells are not identical to murine embryonic stem cells in terms of their characteristics or isolation and maintenance. In view of these differences, one of skill in the art setting out to apply the teachings of Stanford 1 to particular human embryonic stem cell types would have no reasonable expectation of successfully doing so. As such, the combined teachings of Stanford 1 and Stanford 2 fail to satisfy the criteria necessary to render the claimed invention obvious.

Applicants' amendment is not in acquiescence to the rejection. Applicants reserve the right to prosecute claims of similar or differing scope. The cited references fail to teach or suggest each and every limitation of the claimed invention, and thus the cited references fail to undermine the patentability of the claimed invention. Reconsideration and withdrawal of this rejection are respectfully requested.

As Applicants note above in the section of the instant response discussing the status of the claims, Applicants contend that the Examiner has erroneously withdrawn claims 27-32, 35-59, 78-79, 81-88 and 91-93, and that these claims are also presently under consideration. However, given that the Examiner temporarily withdrew claims 27-32, 35-59, 78-79, 81-88, and 91-93 from consideration, the Examiner did not indicate whether or to what extent he would apply the instant rejection to any of these claims. Nevertheless, Applicants note for the record, that the foregoing arguments regarding the patentability of the claimed invention in view of the combined teachings of Stanford 1 and Stanford 2 apply at least equally to temporarily withdrawn claims 27-32, 35-59, 78-79, 81-88, and 91-93. As such, all of the pending claims directed to the elected invention of Group 1 are patentable over Stanford 1 and Stanford 2 for, at least, the reasons outlined above. The combined teachings of Stanford 1 and Stanford 2 fail to satisfy the criteria necessary to undermine the patentability of the claimed invention.

Claim 89 is rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Stanford 1 in view of Stanford 2 and further in view of Odorico *et al.* (Stem Cells, 19:193-204 (2001); hereinafter "Odorico"). Applicants traverse this rejection to the extent that it is maintained in view of the amended claims.

Applicants contend that the cited references fail to satisfy the criteria necessary to render the claimed invention obvious. Nevertheless, to expedite prosecution, Applicants have amended independent claim 67, from which claim 89 depends, to more particularly point out certain embodiments of Applicants' invention. Specifically, Applicants have amended claim 67 to more

particularly point out that the method relates to human stem cells. As amended, claim 67 is directed to the identification of genes that are transcriptionally activated at different times in human stem cells that are differentiating by using a marker DNA construct, wherein the stem cell is an inner mass cell, an embryonic stem cell, an embryonic germ cell, an embryoid body cell, a morula-derived cell, or a partially differentiated embryonic stem cell. The cited references fail to teach or suggest the subject matter of amended claim 67, and on rejected claim 89 which is dependent therefrom. As stated above, Stanford 1 does not teach or suggest a marker DNA in human stem cells, and particularly the identification of genes that are transcriptionally activated at different times in human stem cells that are differentiating by using a marker DNA construct. Stanford 2 and Odorico both fail to cure this deficiency. Therefore, the combined teachings of the cited references fail to undermine the patentability of the rejected claims.

The Examiner alleges that one of skill in the art would have been motivated to modify the cited references to produce the claimed invention because Odorico teaches that embryonic inductive events and complex epithelial-mesenchymal interactions control the formation of organized tissue structures during normal embryogenesis and that these interactions begin to occur in teratomas but are less pronounced during in vitro differentiation (see page 197, column 2). The Examiner further alleges that one of skill in the art would have had a reasonable expectation of success in combining the teachings of Stanford 1 and Stanford 2 with Odorico because these teachings generated successful use of the gene trap technology. Applicants disagree with the Examiner's supposition that the cited references generated successful use of the gene trap technology as it applies to human stem cells. None of the cited references have successfully demonstrated that gene trap technology can be used in human stem cells. Rather, it was Applicants' invention, as described in the instant application, that successfully developed gene trap technology for use in certain human stem cells. At the time of the publication of the cited references, human stem cells were newly isolated. Thus, one of skill in the art at that time would only be learning to isolate, manipulate and maintain human stem cells. There could not have been any expectation of success that the gene trap technology could be used in human stem cells during the differentiation of those cells.

Applicants' amendment is not in acquiescence to the rejection. Applicants reserve the right to prosecute claims of similar or differing scope. For all of the foregoing reasons, the cited

references fail to undermine the patentability of the claimed invention. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 1-2, 11-14, 18 and 33-34 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Stanford 1 in view of Chajut *et al.* (WO 2002/086089, filed 4/23/2002; hereinafter "Chajut"). Applicants traverse this rejection to the extent that it is maintained in view of the amended claims.

Applicants contend that the cited references fail to satisfy the criteria necessary to render the claimed invention obvious. Nevertheless, to expedite prosecution, Applicants have amended claims 1 and 18 (and claims dependent thereon) to more particularly point out certain embodiments of Applicants' invention. Specifically, Applicants have amended the claims to more particularly point out that the methods and compositions of the invention relate to human stem cells, wherein the stem cells are inner mass cells, embryonic stem cells, embryonic germ cells, embryoid body cells, morula-derived cells, or partially differentiated embryonic stem cells. The cited references fail to teach or suggest the subject matter of the amended claims.

As stated above, Stanford 1 does not teach or suggest a marker DNA in human stem cells, and particularly the recited human stem cells. Chajut fails to cure this deficiency. The Examiner has acknowledged that Chajut does not teach methods of identifying genes using the gene trap system (see page 16, last paragraph of the pending Office Action). As such, the combined teachings of the cited references fail to undermine the patentability of the rejected claims.

However, the Examiner alleges that one of skill in the art would have had a reasonable expectation of success in combining the teachings of Stanford 1 and Chajut because each of these teachings generated successful use of the gene trap technology. As stated above, Applicants disagree with the Examiner's supposition that the cited references generated successful use of the gene trap technology, as it applies to human stem cells. None of the cited references have successfully demonstrated that gene trap technology can be used in human stem cells. Chajut, in particular, fails to teach gene trap technology in any type of cell. As such, the combined teachings of Stanford 1 and Chajut fail to satisfy the criteria necessary to render the claimed invention obvious.

Applicants' amendment is not in acquiescence to the rejection. Applicants reserve the right to prosecute claims of similar or differing scope. The cited references fail to teach or

suggest each and every limitation of the claimed invention, and thus the cited references fail to undermine the patentability of the claimed invention. Reconsideration and withdrawal of this rejection are respectfully requested.

As Applicants contend above in the status of the claims, the Examiner has erroneously withdrawn claims 27-32, 35-59, 78-79, 81-88 and 91-93. Nevertheless, for the record, Applicants assert that the above arguments apply equally to these claims. The cited references fail to teach or suggest each and every limitation of these claims, and thus the cited reference fail to satisfy the criteria necessary for render the claims obvious.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000.

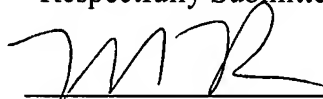
Please charge any deficiency or credit any overpayment in the fees that may be due in this matter to **Deposit Account No. 18-1945**, from which the undersigned is authorized to draw, under **Order No. 103080-P01-029**.

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